JAMA Cardiology | Original Investigation

AAVrh.10hFXN Gene Therapy for the Cardiomyopathy of Friedreich Ataxia
A Nonrandomized Clinical Trial

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IMPORTANCE Friedreich ataxia (FA), a fatal, autosomal recessive disorder caused by pathogenic variants in the frataxin (*FXN*) gene, is characterized by progressive neurologic and cardiac disease, with cardiac disease being the major cause of death. Preclinical studies have demonstrated that systemic administration of AAVrh.10hFXN, an rh.10 serotype cardiotropic adenoassociated virus (AAV) vector expressing the normal human *FXN* coding sequence, reverses the cardiomyopathy in FXN-deficient mice.

OBJECTIVE To assess the safety and preliminary efficacy of administration of AAVrh.10hFXN to adults with FA cardiomyopathy.

DESIGN, SETTING, AND PARTICIPANTS This nonrandomized clinical trial evaluates the pooled data of 2 independent, open-label, dose-escalation trials that used the same gene therapy vector and similar clinical protocols among patients with FA cardiomyopathy at academic medical centers. Data were collected from February 22, 2022, to October 4, 2025, for trial 1 and from February 14, 2023, to September 10, 2025, for trial 2 and analyzed together from November 5, 2025, to March 12, 2026.

INTERVENTION AAVrh.10hFXN, administered intravenously in 3 dose cohorts (1.8×10^{11}, 5.6×10^{11}, and 1.2×10^{12} vector genomes per kilogram of body weight).

MAIN OUTCOMES AND MEASURES In addition to safety as the primary outcome, multiple parameters of exploratory end points were assessed, including cardiac biopsy levels of FXN protein, cardiac magnetic resonance imaging–derived left ventricular mass index (LVMI), and serum high-sensitivity (hs) troponin I.

RESULTS Seventeen patients with FA cardiomyopathy (mean [SD] age, 25 [6] years; 11 [65%] female) were followed up for a mean (SD) of 20 (8) months. There were 4 serious adverse events, 3 possibly related to prednisone immunosuppression and 1 possibly vector-related myocarditis 12 months after therapy, all of which resolved. Other adverse events were transient, nonserious, or not treatment related. In all 8 patients with cardiac biopsy 3 months after therapy, there were higher levels of cardiac FXN (dose cohort 1, 20%; cohort 2, 81%; cohort 3, 123%). After therapy, LVMI was lower by at least 10% in 9 patients and stabilized in 8 patients. Excluding the patient with myocarditis, posttherapy values of serum hs troponin I were lower by at least 10% in 15 patients and higher by at least 10% in 2 patients.

CONCLUSIONS AND RELEVANCE Findings of this nonrandomized clinical trial suggest that intravenous administration of AAVrh.10hFXN was well tolerated and may be a potential treatment for FA cardiomyopathy, as evidenced by preliminary improvement in exploratory efficacy end points.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: NCT05302271 and NCT05445323

Supplemental content

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JAMA Cardiol. 2026;11(8):709-718. doi:10.1001/jamacardio.2026.1699
Published online June 17, 2026. Corrected on August 12, 2026.

Friedreich ataxia (FA), an inherited autosomal recessive ataxia, is a fatal disorder characterized by neurologic and cardiac dysfunction.[1-3] While the progressive neurologic disease limits the ability to ambulate and speak, the cardiomyopathy is responsible for 60% to 65% of deaths.[2,4-7] FA is caused by pathogenic variants in the frataxin (*FXN*) gene on chromosome 9q21.11.[8] *FXN* encodes a protein targeted to mitochondria, where it plays a central role in energy generation.[9-13] *FXN* encodes a 210–amino acid precursor targeted at mitochondria, where it is processed to the 14-kDa mature protein. In the mitochondria, frataxin (FXN) facilitates assembly of iron-sulfur clusters, enabling adenosine triphosphate generation via the electron transport chain complexes I through IV. Most patients with FA (96%) are homozygous for GAA trinucleotide expansion in *FXN* intron 1, which causes transcriptional silencing and leads to a reduction in the levels of FXN.[14,15] The reduced levels of FXN result in loss of mitochondrial iron-sulfur cluster enzyme activity, iron accumulation, increased sensitivity to oxidative stress, and reduced energy generation.[1,10,16-20] The consequences to the heart include stress on cardiomyocytes associated with elevated serum levels of cardiomyocyte structural proteins, such as troponin I.[21-24] As the stress to cardiomyocytes progresses, the result is concentric hypertrophy with increased left ventricular (LV) mass, loss of cardiomyocytes, and fibrosis, leading to heart failure and arrythmias.[2,5,25,26]

Based on this background, augmentation of FXN levels in the heart should be therapeutic, with reduction of the LV hypertrophy and reduction in serum troponin I levels.[6,23,27-29] To assess this hypothesis, based on preclinical efficacy study in FXN-deficient mice,[27,28,30] we treated 17 individuals with FA with AAVrh.10hFXN, an adenoassociated virus (AAV) gene transfer vector composed of the nonhuman primate–derived serotype rh.10 capsid and an expression cassette with a constitutive promoter driving the normal human FXN coding sequence. AAVrh.10hFXN was administered intravenously, a vector and route that in experimental animal models effectively reverses the cardiac pathology associated with FXN deficiency.[27,28,31]

Key Points

Question Is gene therapy with an adenoassociated virus (AAV) coding for human frataxin a safe and preliminary effective therapy for the cardiomyopathy that characterizes Friedreich ataxia?

Findings In an open-label, dose-ranging, nonrandomized clinical trial of 17 patients, intravenous administration of AAVrh.10hFXN was associated with minimal toxic effects, reduced cardiac magnetic resonance imaging assessment of left ventricular mass index, and reduced serum high-sensitivity troponin I level.

Meaning The findings suggest that AAVrh.10hFXN gene therapy is safe, and additional trials are needed to evaluate efficacy for Friedreich ataxia.

Methods

Trial Overview and Oversight

Assessment of the primary end point of safety along with exploratory efficacy parameters of AAVrh.10hFXN treatment of the cardiomyopathy of FA represents the combination of 2 independent nonrandomized clinical trials of 17 patients using similar protocols and the identical AAVrh.10hFXN therapeutic agent. The trial protocols are available in Supplement 1. Trial 1, carried out by the Department of Genetic Medicine at Weill Cornell Medicine (WCM), included 9 individuals with FA. Trial 2, carried out by Lexeo Therapeutics, included 8 individuals with FA. The AAVrh.10hFXN gene therapy vector (referred to as "LX2006" by Lexeo) for both trials was produced by the Belfer Gene Therapy Core Facility, Department of Genetic Medicine, WCM. The 2 trials were carried out with independent regulatory approval. Trial 1 (WCM) was approved and supervised by the WCM Institutional Review Board, the WCM Institutional Biosafety Committee, and the National Heart Lung, and Blood Institute Data and Safety Monitoring Board. Trial 2 (Lexeo) was approved and monitored by the institutional review board and institutional biosafety committee at each site and an independent central data and safety monitoring board. All participants provided written informed consent. The 2 trials had independent US Food and Drug Administration (FDA) Investigational New Drug regulatory approval. Trial 1 (n = 9) was carried out at 1 site (WCM), and trial 2 (n = 8) was carried out at 3 sites (University of South Florida, n = 5; University of California, Los Angeles, n = 1; and Mayo Clinic, n = 2) (eTable 1 in Supplement 2). Data were collected from each participating site; data from trial 1 were stored at WCM, and data from trial 2 were stored at Lexeo. Data were collected from February 22, 2022, to October 4, 2025, for trial 1 and from February 14, 2023, to September 10, 2025, for trial 2 and analyzed together from November 5, 2025, to March 12, 2026.

Study Population

Patients were eligible if they were aged 18 years or older and had a diagnosis of FA with evidence of cardiomyopathy and an *FXN* genotype of intron 1 GAA expansion in both alleles. Patients with early cardiac disease (elevated level of high-sensitivity [hs] troponin I,[32] normal LV mass index [LVMI][33]) and patients with established structural cardiac disease (elevated LVMI[33]) were included. The full inclusion and exclusion criteria are provided in eTables 2 and 3 in Supplement 2. All patients had serum anti-AAVrh.10 neutralizing antibody titers less than 1/100.

Trial Design

Detailed timelines of all parameters are included in the trial protocols (Supplement 1). Trial 1 assessed 23 patients for eligibility and enrolled 9; trial 2 evaluated 17 patients for eligibility and enrolled 8 (eFigures 1 and 2 in Supplement 2). Reasons as to why some screened individuals did not enter the trial (trial 1, 14 of 23 patients; trial 2, 9 of 17 patients) included no evidence of cardiac disease, fibrosis greater than 10%, inability to have cardiac magnetic resonance imaging (cMRI) performed, abnormal liver function, and elevated level of anti-AAVrh.10 neutralizing antibodies.

Table 1. Characteristics of the Study Population Before Therapy[a,b]

Parameter	Trial 1 (n = 9)	Trial 2 (n = 8)	Total (N = 17)
Age, mean (SD) [range], y			
At study entrance	28 (7) [18-35]	23 (4) [18-30]	25 (6) [18-35]
At diagnosis	12 (3) [8-17]	14 (6) [5-20]	13 (5) [5-20]
At 1st symptom	8 (3) [4-12]	11 (5) [5-19]	9 (4) [4-19]
Sex, No. (%)			
Female	6 (67)	5 (62)	11 (65)
Male	3 (33)	3 (38)	6 (35)
GAA repeats, mean (SD) [range], No.			
Allele 1	741 (67) [670-900]	801 (158) [615-1040]	769 (120) [615-1040]
Allele 2	917 (156) [700-1176]	929 (180) [670-1150]	923 (167) [670-1176]
Ambulatory, No. (%)			
Yes	0	6 (75)	6 (35)
No	9 (100)	2 (25)	11 (65)
cMRI			
LVMI, mean (SD) [range], g/m^2[c]			
Men	86 (27) [69-117]	81 (8) [72-86]	84 (18) [69-117]
Women	73 (24) [45-110]	65 (20) [47-100]	70 (22) [45-110]
Inferolateral wall thickness, mean (SD) [range], cm	1.0 (0.2) [0.7-1.4]	0.8 (0.1) [0.6-1.0]	0.9 (0.2) [0.6-1.4]
Ejection fraction, mean (SD) [range], %	62 (11) [35-78]	65 (4) [58-72]	64 (9) [35-78]
Fibrosis, mean (SD) [range], %	1.0 (1.0) (0.0-3.0)	1.3 (2.4) (0.0-6.8)	1.2 (1.9) [0.0-6.8]
Serum high-sensitivity troponin I, mean (SD) [range], ng/L[d]	663 (857) [7-2524]	127 (216) [11-650]	410 (714) [7-2524]
Anti-AAVrh.10FXN neutralizing antibody titer	<100^{-1}	<100^{-1}	<100^{-1}
Patients in dose cohort, No. (%)			
1.8 × 10^{11} vg/kg	5 (56)	1 (12)	6 (35)
5.6 × 10^{11} vg/kg	4 (44)	3 (38)	7 (41)
1.2 × 10^{12} vg/kg	0	4 (50)	4 (24)

Abbreviations: cMRI, cardiac magnetic resonance imaging; LVMI, left ventricular mass index; vg/kg, vector genomes per kilogram of body weight.

[a] No patient had an implantable cardiovascular defibrillator; for a list of Friedreich ataxia–relevant medications, see eTable 4 in Supplement 2.

[b] The self-reported race of all 17 patients was White. Race was provided by participants as part of demographic data collection on trial participants.

[c] The reference ranges for LVMI range are 39 to 85 g/m^2 for men and 30 to 68 g/m^2 for women.[33]

[d] The reference ranges for serum high-sensitivity troponin I are 58 ng/L or less for men and 40 ng/L or less for women.[32]

Both trials 1 and 2 had an open-label design with ascending doses, including 1.8 × 10^{11}, 5.6 × 10^{11}, and 1.2 × 10^{12} vector genomes per kilogram of body weight (**Table 1**). The vector was administered intravenously over 1 hour. Immunosuppression with prednisone was similar in the 2 trials, starting before therapy and completing after 14 weeks (see trial protocols in Supplement 1). A list of other FA-relevant medications being received by the study population is provided in eTable 4 in Supplement 2. Unrelated to this study, several patients were administered omaveloxolone by their treating neurologist for the neurologic manifestations of FA.[34,35] These patients and the timing of omaveloxolone administration are indicated in the data regarding modified Friedreich Ataxia Rating Scale (mFARS) neurologic elevation and liver toxic effect parameters.

Assessments

The primary end point was safety, with exploratory end points focused on efficacy parameters (eTable 5 in Supplement 2). The 17 patients were assessed periodically (eTable 6 in Supplement 2; trial protocols in Supplement 1). Safety was assessed via numerous parameters, including periodic routine blood and urine studies, liver ultrasonography, electrocardiography, and Holter monitoring. Based on a review of the literature,[6,23,36-38] the exploratory end points relevant to efficacy included periodic cMRI assessment of the LVMI[33] and serum levels of hs troponin I.[32] These parameters are particularly relevant to FA, in which the cardiomyopathy is the leading cause of mortality.[2,4-7] The LVMI provides a sensitive marker of myocardial remodeling, while hs troponin I reflects ongoing cardiomyocyte stress and injury, both of which are critical for monitoring cardiac involvement in FA.[3,36,38] For details regarding cMRI acquisition and analysis, see the studies by Janik et al,[39] Codella et al,[40] and Simprini et al[41] for trial 1 and by Kawel-Boehm et al[33] for trial 2.

Additional exploratory parameters included cMRI quantification of lateral wall thickness, ejection fraction, and serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Trial 2 included cardiac biopsy assessment of FXN protein levels assessed before therapy and 3 months after therapy (eAppendix 1 in Supplement 2). Additional exploratory end points included assessment with the mFARS neurologic scale.[42,43] Details of all end points and safety parameters are provided in the trial protocols in Supplement 1.

Vector Design

AAVrh.10hFXN is composed of the AAVrh.10 capsid encoding AAV2 inverted terminal repeats flanking the human cytomegalovirus enhancer/promoter, a splice donor and the left-hand intron sequence from chicken β-actin, the right-hand

Table 2. Adverse Events (AEs) Associated or Possibly Associated With AAVrh.10hFXN and/or Prednisone Immunosuppression[a]

Event	Events, No. (patients, No. [%])	Trial[b]	Dose cohort[c]	Association with vector and/or prednisone
SAE				
Myocarditis	1 (1 [6])	2	2	Possibly associated with vector
Streptococcal A infection	1 (1 [6])	1	2	Possibly associated with prednisone
Pneumonia	1 (1 [6])	2	2	Possibly associated with prednisone
Chest pain, hospitalization	1 (1 [6])	2	2	Possibly associated with prednisone
AE				
Leukocytosis	3 (3 [18])	1	1, 2	Possibly associated with vector or prednisone
Psychiatric	4 (4 [24])	1, 2	1, 2	Possibly or probably associated with prednisone
Genitourinary	2 (2 [12])	1, 2	1, 3	Possibly or probably associated with prednisone
Systemic	6 (5 [30])	1, 2	1, 2, 3	Probably or definitely associated with prednisone
Anemia	1 (1 [6])	1	2	Possibly associated with vector
Cardiovascular	3 (2 [12])	1, 2	2	Probably or definitely associated with prednisone
Elevated liver enzyme levels	2 (1 [6])	2	3	Probably associated with vector
Gastrointestinal	1 (1 [6])	1	2	Probably associated with prednisone
Headaches	1 (1 [6])	2	2	Possibly associated with prednisone
Increased NT-proBNP level	3 (3 [18])	1, 2	2	Possibly associated with vector or prednisone
Increased troponin T level	1 (1 [6])	2	2	Possibly associated with vector
Pulmonary	2 (1 [6])	2	2	Possibly associated with prednisone
Dermatologic	14 (4 [24])	1, 2	2, 3	Probably or definitely associated with prednisone
Musculoskeletal	2 (2 [12])	2	2, 3	Possibly associated with prednisone
All SAEs related to vector	1 (1 [6])	...	...	...
All SAEs related to prednisone	3 (3 [18])	...	...	...
All AEs related to vector	8 (6 [36])	...	...	...
All AEs related to prednisone	39 (12 [70])	...	...	...
All AEs related to vector and/or to prednisone	46 (14 [82])	...	...	...

Abbreviations: NT-proBNP, N-terminal pro–B-type natriuretic peptide; SAEs, serious adverse events; ellipsis, not applicable.

[a] SAEs and AEs that were reported from the time at which the first patient received a dose (trial 1; July 2022) until the data cutoff date (January 6, 2026) and were considered by the investigators to be associated or possibly associated with the AAVrh.10hFXN vector or 14-week immunosuppression with prednisone are listed. Additional details are provided in the trial protocols in Supplement 1. See eTable 7 in Supplement 2 for details regarding each category.

[b] Trial 1 is the Weill Cornell Medicine trial (n = 9); trial 2, the Lexeo trial (n = 8).

[c] Dose cohort 1 received 1.8×10^{11} vector genomes per kilogram of body weight (vg/kg); dose cohort 2, 5.6×10^{11} vg/kg; and dose cohort 3, 1.2×10^{12} vg/kg.

intron sequence and splice acceptor from rabbit β-globin, an optimized Kozak sequence, the human FXN coding sequence, and a rabbit β-globin polyA sequence (eFigure 3 in Supplement 2).

Statistical Analysis

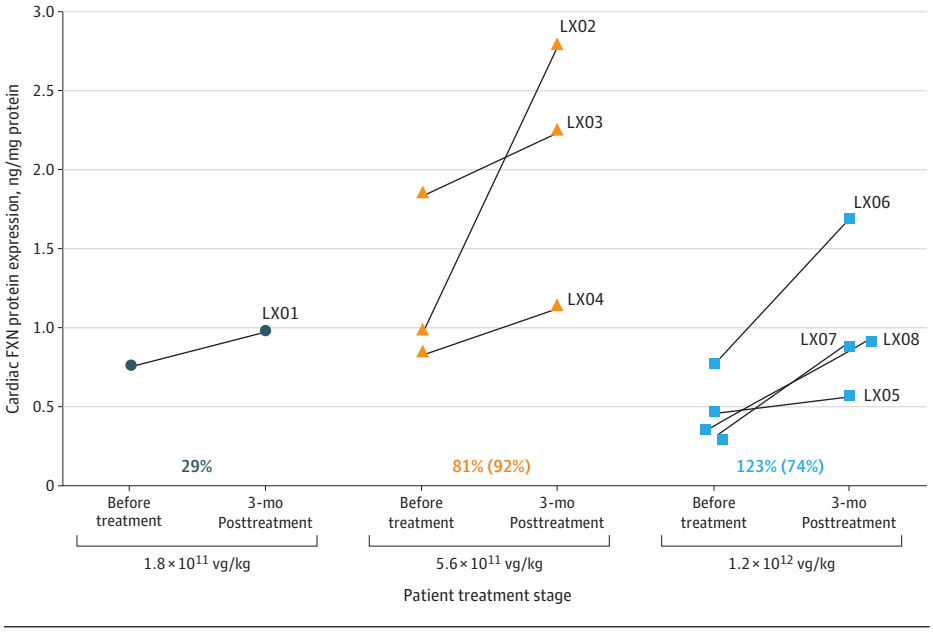
The primary end point was safety. The exploratory end points of cardiac-related efficacy were assessed by cMRI quantification of the LVMI and serum hs troponin I level. Safety assessments were as detailed in the clinical protocols, analyzed per assessment point to determine whether they are in the reference range per performing laboratory. Categorization of adverse events (AEs) and serious AEs (SAEs) were as detailed in the protocols based on FDA guidance documents.[44,45] To assess the exploratory end points, a linear mixed-effects model was applied to the parameters over time, with specific focus on LVMI and quantification of the serum hs troponin I level. Repeated observations of patients over time were modeled as a random effect, and month of assessment was modeled as a fixed linear factor. The other factors in the linear mixed-effects model were sex, age at therapy, trial, dose, and maximum GAA repeats, all included as fixed effects. Estimation used all patients both including and excluding patient LX03, who developed myocarditis at month 12 after therapy and required hospitalization. All analyses are descriptive. Results are reported as point estimates with 95% CIs. The widths of the CIs have not been adjusted for multiplicity and should not be used to infer treatment effects. Although intravenous AAVrh.10hFXN therapy is focused on the cardiac manifestations of FA, based on the knowledge that systemic administration of AAVrh.10hFXN also targets skeletal muscle,[46] the linear mixed-effects model was also applied to the periodic assessment with the mFARS, a neurologic scale used to assess patients with FA.[42,43] All statistical analyses were conducted using R version 4.5.1 software (R Foundation).

Results

Patient Characteristics

In the 2 trials, a total of 40 patients with FA were assessed for eligibility (eFigures 1 and 2 in Supplement 2); among them, 17

Figure 1. Cardiac Frataxin (FXN) Levels Before and 3 Months Following AAVrh.10hFXN Therapy



Cardiac FXN levels before and after therapy are shown for each dose group. Below each graph is the mean (SD) percentage increase in cardiac FXN levels for each dose (doses are given as vector genomes per kilogram of body weight [vg/kg]). The FXN levels were measured by liquid chromatography–mass spectroscopy. LX and identifier numbers indicate the patient numbers from trial 2 (Lexeo trial).

patients (mean [SD] age, 25 [6] years; 11 [65%] female) were treated with AAVrh.10hFXN. As detailed in Table 1, the patients in the 2 trials were similar except for ambulatory status (trial 1, 0 of 9 patients; trial 2, 6 of 8 patients). Patients were excluded from treatment mostly because they did not meet the inclusion criteria or met the exclusion criteria. The mean (SD) follow-up was 20 (8) months (range, 6-36 months). No treated patients were lost to follow-up.

Safety

No patients withdrew because of AEs, and there were no deaths. The therapy with AAVrh.10hFXN and 14-week immunosuppression with prednisone was generally well tolerated, with 4 SAEs possibly associated with the vector or prednisone (**Table 2**; eAppendix 2 and eTable 7 in Supplement 2). Patient LX03 developed asymptomatic myocarditis at month 12, possibly related to the vector. For this patient, it was not possible to distinguish the contribution of the gene therapy vs the myocarditis to the LVMI and hs troponin I level, so exploratory analysis was conducted both including and excluding data from this patient. The other 3 SAEs were possibly related to prednisone immunosuppression. There were no SAEs related to liver toxic effects or complement activation. There were a total of 46 AEs possibly related to the vector, prednisone, or both (Table 2; eTable 7 in Supplement 2). Most AEs did not require therapy or resolved with transient conventional therapy. There were a variety of AEs not associated with either vector or prednisone (eTables 8 and 9 in Supplement 2). Other than a rare value outside the reference range, there were no significant abnormalities after therapy in serum assessment of liver function in either trial, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, prothrombin time, activated partial thromboplastin time, or α-fetoprotein (eFigure 4 in Supplement 2). Following vector administration, platelet levels remained normal. There were minimal fluctuations in serum C3 and C4 levels (eFigures 4 and 5 in Supplement 2). One patient in trial 1's dose cohort 2 had a transient decrease in serum C3 and C4 levels at week 2; there was no clinical evidence of thrombotic microangiopathy. There were no electrocardiographic changes after therapy. Holter monitoring showed minimal atrial or ventricular arrhythmias at baseline, with no increase following therapy.

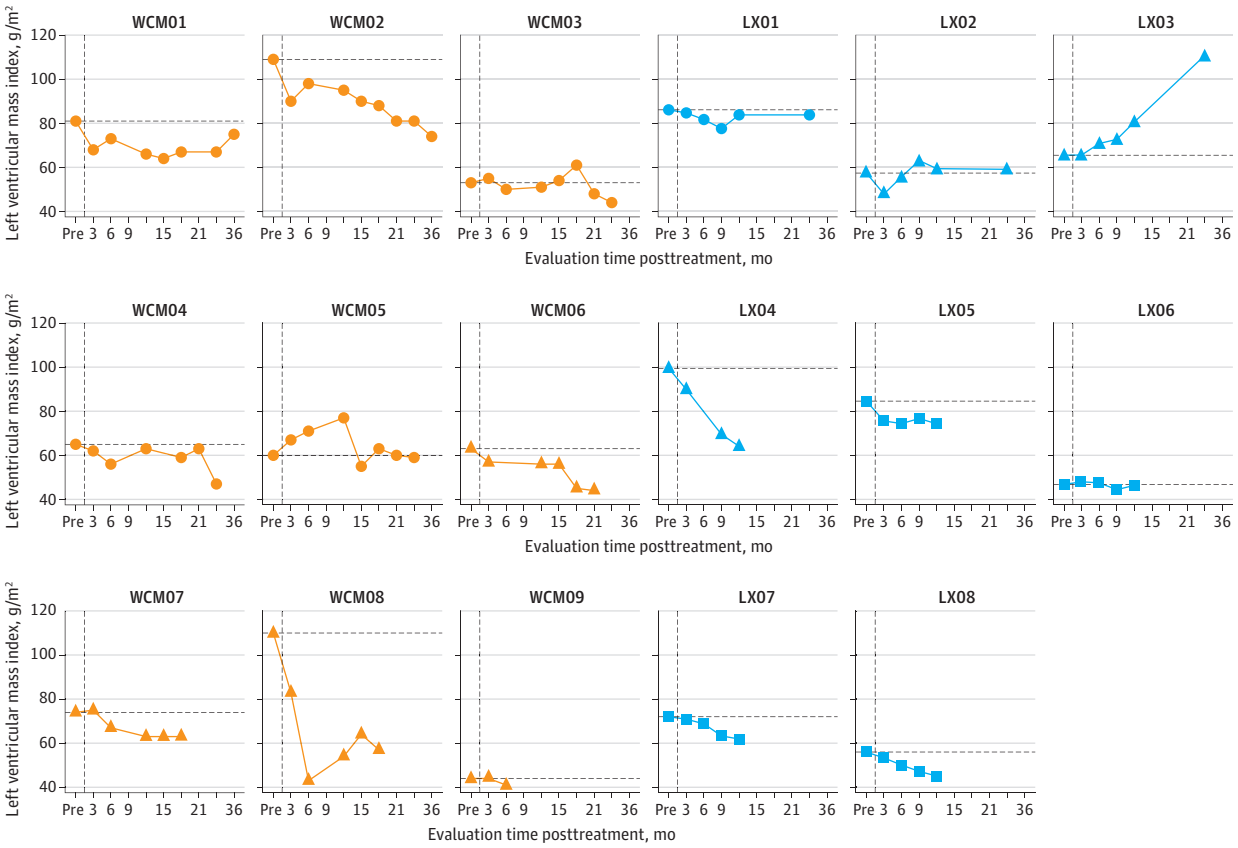
Cardiac Expression of FXN

Cardiac biopsy was carried out before therapy and 3 months after therapy in the 8 patients in trial 2 only (**Figure 1**). All 8 patients had higher cardiac FXN levels at 3 months after therapy.

cMRI LVMI and Serum hs Troponin I Level

Based on the literature regarding FA cardiomyopathy,[6,23,36-38] we focused the analyses on the exploratory end points of cardiac MRI LVMI and serum hs troponin I level. The graph of LVMI before and after therapy for all 17 patients is shown in **Figure 2**, the percentage change from before therapy in eFigure 6 in Supplement 2, and the actual values at each time point in eTable 10 in Supplement 2. Qualitative assessment comparing the mean LVMI from before to after therapy among the 17 patients suggested that 9 patients had a lower LVMI, 7 had a stabilized LVMI, and 1 (patient LX03, with myocarditis) had a higher LVMI. Statistical analysis using a linear mixed-effects model to test the association of AAVrh.10hFXN therapy with LVMI after therapy, taking into account all posttherapy LVMI values and fixed-effect parameters month, trial, sex, dose, age at therapy, and GAA long repeats, showed reduction both when excluding patient LX03 (including all fixed-effects; mean monthly change, −0.50 g/m^2; 95% CI, −0.71 to −0.29 g/m^2) and when including patient LX03 (mean monthly change, −0.35

Figure 2. Cardiac Magnetic Resonance Imaging Quantification of the Left Ventricular Mass Index Before and After Therapy for Each Patient



For each treated patient, the left ventricular mass index is shown before therapy (Pre) and at multiple points after therapy (3, 6, 9, 12, 15, 18, 21, 24, and 36 months). The 9 patients in trial 1 (Weill Cornell Medicine [WCM] trial, with patient numbers WCM01-WCM09) are shown in orange; the 8 patients in trial 2 (Lexeo trial, with patient numbers LX01-LX08) are shown in blue. The vertical dashed line indicates the time of therapy; horizontal dashed line, the pretherapy value. The dose cohorts were 1.8×10^{11} vector genomes per kilogram of body weight (vg/kg) (circles), 5.6×10^{11} vg/kg (triangles), and 1.2×10^{12} vg/kg (squares). The reference ranges for the left ventricular mass index are 39 to 85 g/m^2 for men and 30 to 68 g/m^2 for women.[33]

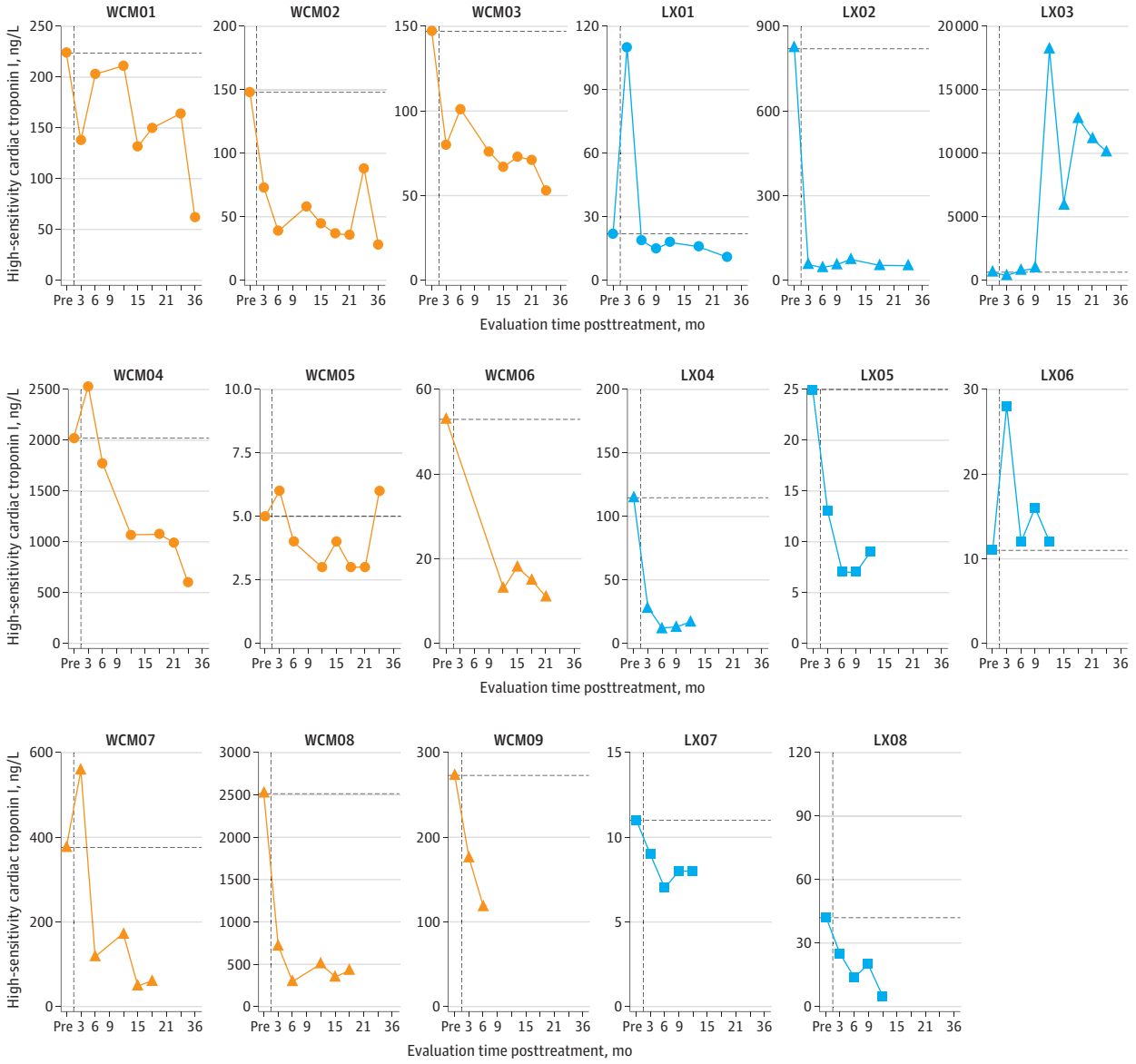
g/m^2; 95% CI, −0.59 to −0.11 g/m^2) (eTables 10 and 11 in Supplement 2). There was no association of lower LVMI with patients also treated with omaveloxolone, cardiac drugs, or antioxidants. Comparison of LVMI before and after therapy assessed by cMRI vs LVMI assessed by echocardiography demonstrated similarity (eFigure 7 in Supplement 2).

As has been previously reported,[36,37] most patients with FA cardiomyopathy have high serum levels of hs troponin I, reflecting ongoing stress to cardiomyocytes. This was true for the 17 treated patients, with 12 having a high serum hs troponin I level before therapy (among those with a high pretherapy hs troponin I level, the group mean [SD] hs troponin I level was 616 [780] ng/L). In most patients, AAVrh.10hFXN therapy resulted in a markedly lower serum hs troponin I level (**Figure 3**; eFigure 8 in Supplement 2). Qualitative assessment suggested that 15 patients had mean hs troponin I levels that were at least 10% lower after therapy (eTable 12 in Supplement 2). Statistical analysis using the linear mixed-effects model taking into account all of the fixed-effect parameters demonstrated no significance (mean monthly change, 44.6 ng/L; 95% CI, −5.5 to 94.6 ng/L) when patient LX03 was included (as expected, since the myocarditis evoked a serum hs troponin I level as high as 18 214 ng/L at month 12). However, when patient LX03 was excluded from the analysis, the mean hs troponin I level was markedly lower (mean monthly change, −13.7 ng/L; 95% CI, −20.9 to −6.4) (eTable 13 in Supplement 2). Excluding patient LX03, when the pretherapy vs last posttherapy values of LVMI and serum hs troponin I level were compared, 13 of 16 treated patients had lower values in both parameters (eFigure 9 in Supplement 2). There was no association of lower serum levels of hs troponin I with patients also treated with omaveloxolone, cardiac drugs, or antioxidants.

Additional Secondary and Exploratory Outcomes

A variety of additional exploratory cMRI parameters were assessed before and after therapy. Lateral wall thickness was lower (eFigure 11 and eTable 14 in Supplement 2). In patients with baseline normal ejection fraction, it remained stable after therapy. In the 1 patient with a low baseline ejection fraction (patient WCM08), there was an increase in ejection fraction from 35% at baseline to 74% by 18 months after therapy (eFigure 10 and eTable 15 in Supplement 2). Percentage of fibrosis remained

Figure 3. Serum High-Sensitivity Troponin I Levels Before and After Therapy for Each Patient



For each patient, the high-sensitivity troponin I level is shown before therapy (Pre) and at multiple points after therapy (3, 6, 9, 12, 15, 18, 21, 24, and 36 months). The 9 patients in trial 1 (Weill Cornell Medicine [WCM] trial, with patient numbers WCM01-WCM09) are shown in orange; the 8 patients in trial 2 (Lexeo trial, with patient numbers LX01-LX08) are shown in blue. The vertical dashed line indicates the time of therapy; horizontal dashed line, the pretherapy value. The dose cohorts were 1.8×10^{11} vector genomes per kilogram of body weight (vg/kg) (circles), 5.6×10^{11} vg/kg (triangles), and 1.2×10^{12} vg/kg (squares). The reference ranges for high-sensitivity troponin I are 58 ng/L or lower for men and 40 ng/L or lower for women.[32]

stable in 14 of 17 patients, with minor higher levels in 3 of the 17 patients (eFigure 12 in Supplement 2). Among the 17 patients, 5 had an elevated NT-proBNP level at baseline; 4 of these 5 patients had a lower value after therapy. Of the other 12 patients, the NT-proBNP level remained stable, mostly in the reference range, in 10 patients; among the 10 patients, 2 (including patient LX03) had an increased NT-proBNP level after therapy (eFigure 14 in Supplement 2). In most patients, the creatine phosphokinase level remained stable, mostly in the reference range (eFigure 13 in Supplement 2). Periodic assessment by Holter monitoring demonstrated no increase in atrial or ventricular arrhythmias after therapy.

Systemic administration of AAVrh.10hFXN was associated with stabilization over time of scores on the mFARS, a scale used to assess the progression of FA neurologic disease (eFigure 15 and eTables 16 and 17 in Supplement 2). This is of interest in that a natural history study of untreated patients with FA showed a worsening of mFARS scores over time.[47] While our trials did not have a contemporaneous untreated control group, it is possible that systemic administration of

AAVrh.10hFXN could be useful in treating the neurologic disease. In this context, while little systemic AAVrh.10 administration distributes to the brain, a significant amount does distribute to skeletal muscle,[46] and the stabilization of the mFARS score could be secondary to delivery of FXN to skeletal muscle.

Discussion

FA manifests as neurologic and cardiac disease. While the neurologic disease is debilitating, we focused our therapy on the cardiac disease, which is the major cause of death.[2,4-7] The pathogenesis of FA cardiac disease develops from cardiomyocyte FXN deficiency and the consequential deficit of energy generation. The resulting stress on the cardiomyocyte is initially manifested by elevations in serum levels of cardiomyocyte structural proteins, such as hs troponin I. As the stress caused by FXN deficiency continues, the cardiomyocytes hypertrophy in an attempt to maintain normal cardiac function, eventually causing clinical cardiac hypertrophy identified by increased LVMI. The myocardial hypertrophy typically develops with preserved systolic function, but as the disease progresses, there is contractile dysfunction, fibrosis, and eventual death.[26,38,48]

A well-grounded rationale exists to support the use of AAVrh.10hFXN gene therapy as a strategy to reverse the cardiac manifestation of FA, including the following: (1) FA is a slowly progressive disorder with known target cells (cardiomyocytes)[7,49]; (2) there is a known genetic etiology and understood pathogenesis[14,15]; (3) FA-associated LV hypertrophy is reversible in experimental studies in animals[27,28,31]; (4) intravenous administration of the AAVrh.10 gene transfer is effective at transferring the FXN coding sequence to cardiomyocytes[27,28,31]; (5) FXN expression is ubiquitous in all organs, minimizing risk for off-target effects[50]; and (6) proof of concept has been established in 2 independent FA cardiac gene knockout models treated with AAVrh.10hFXN.[27,28,31]

Cardiomyopathy is the cause of death in 60% to 65% of individuals with FA.[2,4-7] Almost all patients with FA have abnormal electrocardiographic findings.[7,51] Heart failure and arrhythmias are common causes of cardiac-related death.[2,4-7] Longer (GAA) triplet repeat lengths and higher rates of arrhythmia and dilated cardiomyopathy are associated with increased mortality.[2,52] Pathologically, cardiac involvement eventually manifests as concentric hypertrophy rapidly followed by fibrosis without significant impairment of contractile function, progressing later to decreased systolic function or hypertrophic changes followed later by end-stage cardiomyopathy.[2,25] Imaging studies have shown that patients with FA eventually develop increased LV mass (hypertrophy), despite normal blood pressure (afterload).[5,49] The severity of LV hypertrophy is associated with genotype, with a correlation between LV mass and GAA repeat number.[53] LV hypertrophy provides a pathophysiologic substrate for ultimate development of fibrosis, which results from cell death in the context of altered mitochondrial function or hypertrophy-induced impairments in LV perfusion and increased LV stress.[54]

Based on this background, we initiated clinical studies to assess the hypothesis that systemic administration of AAVrh.10hFXN to patients with FA cardiomyopathy would be safe and reduce LVMI, thus improving the cardiac remodeling that characterizes FA heart disease and reducing the elevated serum hs troponin I level, a biomarker of cardiomyocyte injury. In this study, we included patients with early manifestations of FA cardiac disease (elevated serum hs troponin I level, normal findings on cMRI assessment of LVMI) and patients with more advanced disease who had an elevated LVMI. In regard to safety, at the doses tested (ranging from 1.8×10^{11} to 1.2×10^{12} vector genomes per kilogram of body weight) and with transient (14-week) immunosuppression with prednisone, there were minimal toxic effects. Other than the SAE of myocarditis in 1 patient 12 months after therapy possibly associated with the vector, which resolved with corticosteroid therapy, the other 3 SAEs were possibly associated with the immunotherapy. The AEs possibly associated with the therapy were transient and, when necessary, treated with conventional therapy.

The 2 parameters most sensitive to FA cardiac disease are cMRI assessment of LVMI and serum hs troponin I level.[6,23,36-38] Excluding the patient who developed myocarditis, periodic posttherapy quantification of LVMI and hs troponin I level demonstrated reduction after therapy. AAVrh.10hFXN therapy was associated with stabilization of the mFARS neurologic scale score, suggesting that the gene therapy may also be therapeutic for the musculoskeletal and/or neurologic manifestations of FA; comparing this in treated patients vs untreated control individuals is of interest for future study.

Limitations

Although the preliminary efficacy data are encouraging, there are limitations to the study. As is typical for most hereditary disorders, the sample size was small and the treated participants were used as their own controls. Also, most of the participants had early cardiac dysfunction, and it will be of interest to assess the effects of AAVrh.10hFXN therapy on individuals with a broad spectrum of the disease.

Conclusions

This nonrandomized clinical trial found that intravenous administration of AAVrh.10hFXN was well tolerated and is a potential treatment for FA cardiomyopathy, as evidenced by preliminary improvement in exploratory efficacy end points. Further studies are needed to evaluate the efficacy of this therapeutic approach.

ARTICLE INFORMATION

Accepted for Publication: April 5, 2026.

Published Online: June 17, 2026. doi:10.1001/jamacardio.2026.1699

Correction: This article was corrected on August 12, 2026, to add open access status; the open access license is CC-BY-NC-ND.

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Obtained funding: Crystal, Kaminsky, Gavrilova.
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Conflict of Interest Disclosures: Dr Crystal reported grants from the National Heart, Lung, and Blood Institute (NHLBI) and consulting fees, royalties, stock, and stock options from Lexeo Therapeutics during the conduct of the study; and consulting fees, royalties, stock, and stock options from Lexeo Therapeutics outside the submitted work; in addition, Dr Crystal has a patent for 10224-04-US pending for Lexeo Therapeutics. Dr Weinsaft reported consulting fees from Lexeo Therapeutics, Adverum Biotechnologies, and AAVLIFE and a grant from the National Institutes of Health during the conduct of the study; and consulting fees from Faction Imaging outside the submitted work. Dr Kaminsky reported salary from the NHLBI and royalties and equity from Lexeo Therapeutics during the conduct of the study; and royalties and equity from Lexeo Therapeutics outside the submitted work; in addition, Dr Kaminsky had a patent for Methods for Treating FA pending for Lexeo Therapeutics. Dr Patel reported serving on an advisory board for Lexeo Therapeutics during the conduct of the study; and serving on an advisory board for Lexeo Therapeutics outside the submitted work. Dr Kaner reported grants from Weill Cornell Medicine during the conduct of the study. Dr Sarva reported clinical trial support from Blue Rock, Prevail, Insightec, Novo Nordisk, Biogen, Bukwang, Biohaven, Genentech, Meira, Vima, Cerevance, Neuroderm, UCB, Sun Pharma, Bial, and Iregene and advisory board fees from Novo Nordisk and Neuroderm outside the submitted work. Dr Sondhi reported equity from Lexeo Therapeutics during the conduct of the study; in addition, Dr Sondhi had a patent application with royalties paid for Methods for Treating FA. Dr Aubert reported personal fees, salary, stock, and stock options from Lexeo Therapeutics during the conduct of the study. Dr Khan reported personal fees, salary, stock, and stock options from Lexeo Therapeutics during the conduct of the study; and personal fees, salary, stock, and stock options from Lexeo Therapeutics outside the submitted work. Dr Selvan reported salary, stock, and stock options with Lexeo Therapeutics during the conduct of the study. Dr Bhalla reported salary, stock, and stock options with Lexeo Therapeutics during the conduct of the study. Dr Adler reported personal fees, salary, stock, and stock options from Lexeo Therapeutics, Myoventive, and Rocket Pharmaceuticals and grants from the California Institute for Regenerative Medicine outside the submitted work. Dr Zesiewicz reported grants from the University of South Florida and research funding and advisory board fees from Lexeo Therapeutics during the conduct of the study; and research funding and advisory board fees from Lexeo Therapeutics outside the submitted work. No other disclosures were reported.

Funding/Support: The WCM trial (trial 1) was funded by grant HL151355 from the NHLBI. The Lexeo trial (trial 2) was funded by Lexeo Therapeutics.

Role of the Funder/Sponsor: The NHLBI had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Lexeo Therapeutics had a role in the design and conduct of the Lexeo trial (trial 2); collected and managed data in the Lexeo trial (for which analysis was done by Weill Cornell Medicine) and commented on interpretation of the data; had no role in the preparation of the manuscript; reviewed and approved the manuscript; and participated in the group decision of all authors to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank N. Mohamed, MPH (Department of Genetic Medicine, Weill Cornell Medical College), for editorial support; no compensation was received beyond usual salary.

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